Paper No. 31

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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Ex parte JEAN-NOEL DENIS, ANDREW-ELLIOT GREENE and
ALICE KANAZAWA

_____

Appeal No. 2001-0694
Application No. 08/908,807

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ON BRIEF

_____

Before WILLIAM F. SMTIH, GRIMES, and GREEN, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 17-21. Claim 17 is representative of the claims on appeal, and a copy of that claim may be found appended to this decision.

The examiner relies upon the following references:

Bourzat et al. (Bourzat I)	5,476,954	December 19, 1995
Kelly et al. (Kelly)	5,556,878	September 17, 1996
Mas et al. (Mas)	5,677,462	October 14, 1997
Commercon et al. (Commercon I)	5,637,723	June 10, 1997
Commercon et al. (Commercon II)	5,726,318	March 10, 1998
Bourzat et al. (Bourzat II)	WO 92/09589	June 11, 1992

Commercon et al., "Improved Protection and Esterification of a Precursor of the Taxotere and Taxol Side Chains," Tetrahedron Letters, Vol. 33, No. 36, pp. 5185-5188 (1992) (Commercon III).

The claims stand rejected under as being rendered obvious by Bourzat II, Commercon III and Kelly. Claims 17-21 are also subject to a double-patenting rejection over claims 1-3 of Mas, claim 29 of Commercon I, claims 1 and 2 of Commercon II and claim 13 of Bourzat I. After careful review of the record on appeal, we reverse.

BACKGROUND

Taxanes are a promising group of chemotherapeutics currently in various clinical trials for treating cancers. Taxanes are stereochemically complicated molecules, having at least 11 stereocenters. According to the Appeal Brief, the side chain at position 13 is of particular importance, as that side chain is generally coupled to a baccatin precursor to form the desired taxane derivative. The side chain has two stereocenters, thus there are four possible isomers, in two enantiomeric pairs. See Appeal Brief, pages 2-3.

According to the Appeal Brief, only one of the isomers of the position 13 is clinically interesting—the 2'R,3'S isomer. See id. Therefore, synthetic methods have centered on synthesizing the position 13 sidechain in a stereospecific manner. Thus, the Appeal Brief states that prior art methods focused on the use of an oxazolidine ring to add that sidechain, wherein the ring had the same stereochemistry as that desired in the position 13 side chain, i.e., the prior art focused on the use of a 4S,5R oxazolidine. See id. at 3.

The specification teaches synthesis of taxane derivatives, wherein an oxazolidine as claimed in claim 17 is used. See Specification, pages 7-8. The claimed oxazolidine differs from the prior art in that it does not have the stereochemistry of the side chain in the taxane derivative, i.e., the oxazolidines used in prior art syntheses are the 4S,5R isomer, whereas the claimed oxazolidine is the 4S,5S isomer. See id. at 8. According to the specification, the desired taxane derivatives "can be obtained, with a stereoselectivity in the region of 100%," in a synthetic method utilizing the claimed 4S,5S isomers. Id. at 7.

DISCUSSION

The examiner has rejected claims 17-21, i.e., all the pending claims, as being rendered obvious by Bourzat II, Commercon III or Kelly. The claims were also subject to a double-patenting rejection over claims 1-3 of Mas, claim 29 of Commercon I, claims 1 and 2 of Commercon II and claim 13 of Bourzat I.

With respect to the double patenting rejection, the patents relied upon all claim the 4R,5S oxazolidine isomer. According to the examiner,

> [t]he disclosure of one isomer would suggest the other(s). Therefore, the instant claimed oxazolidine compounds would have been suggested to one skilled in the art.

Examiner's Answer, page 4.

Basically the same reasoning is used in the obviousness rejection under 35 U.S.C. ' 103(a). Due to its brevity, the entire rejection is reproduced below.

> Appellants claim oxazolidine compounds. [Bourzat II] (page 2), [Commercon III] (page 5186) and Kelly (column 11) each teach oxazolidine compounds. The difference between the compounds of the prior art and the compounds instantly claimed is that the prior art teaches a different isomer than that which is instantly claimed.
>
> One stereoisomer would suggest the other(s). One skilled in the art would have been motivated to prepare compounds embraced by the reference genera with the expectation of producing oxazolidine compounds which would be useful in preparing taxane derivatives. Therefore, the instant claimed compounds would have been suggested to one skilled in the art.

Answer at page 5.

Appellants contend, in response to the above rejection, that the Examiner has failed to make out a prima facie case of obviousness. Specifically, Appellants argue that the rejection has provided no reasoning of how any of the references relied upon, either for the double patenting rejection or the obviousness rejection, "teach or suggest the desirability of the selective alteration of only one chiral center (to the exclusion of the other chiral centers)," to arrive at the claimed compounds. We agree.

The burden is on the examiner to set forth a prima facie case of obviousness. See In re Alton, 76 F.3d 1168, 1175, 37 USPQ2d 1578, 1581 (Fed. Cir. 1996). In order to make a prima facie case of obviousness based on the structural similarity, in this case the isomerism, between the claimed compound and the compound disclosed by the prior art, not only must the structural similarity exist, but the prior art must also provide reason or motivation to make the claimed compound. See In re Dillon, 919 F. 2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc), In re Mayne, 104 F. 3d 1339, 1341, 41 USPQ2d 1451, 1454 (Fed. Cir. 1997); In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 256 (CCPA 1979). Moreover, the prior art has to enable the ordinary artisan to make the claimed compound. See Payne, 606 F.2d at 314.

In the rejection above, the examiner states that "[o]ne skilled in the art would have been motivated to prepare compounds embraced by the reference genera with the expectation of producing oxazolidine compounds which would be useful in preparing taxane derivatives," but does not set forth any facts or findings to support the motivational statement. See In re Lee, 2002 U.S. App. LEXIS 855, *12 (Fed. Cir. Jan. 18, 2002) (in reviewing an obviousness rejection, the court noted that "conclusory statements" as to teaching, suggestion or motivation to arrive at the claimed invention "do not adequately address the issue."). The stereochemistry of the sidechain at position 13 of the taxane derivatives appears to be important for pharmacological function, and all the prior art cited by the examiner utilizes an oxazolidine precursor to the sidechain that preserves the stereochemistry of the

side chain. Admittedly, while the Kelly reference teaches the use of an oxazolidine in which the stereochemistry is not defined, see Kelley, Col. 11, Formula 7, and teaches that "[b]oth oxazolidine isomers are equally effective" in the production of taxol analogs, see id. at col. 12, lines 62-64, in the reaction charts, when the stereochemistry of the oxazolidine is defined, the 4R,5S isomer is used, see id. at col. 80, compound B-3. The rejection sets forth no facts or findings that the ordinary artisan would have known how to use the 4R,5S oxazolidine to produce taxane derivatives. Finally, although not contested by Appellants, the rejection does not set forth any facts or findings that the prior art enables the ordinary artisan to synthesize the claimed compounds.

Thus, the rejection of claim 1-21 under 35 U.S.C. ' 103(a) over Bourzat II, Commercon III and Kelly, as well as the double-patenting rejections over claims 1-3 of Mas, claim 29 of Commercon I, claims 1 and 2 of Commercon II and claim 13 of Bourzat I, is hereby reversed.

OTHER MATTERS

There is some ambiguity in the record as to what diastereomers are encompassed by the teachings of Kelly.

As stated above, the Kelly reference teaches oxazolidine compounds of unspecified stereochemistry. See Kelly, Col. 11, Formula 7. Kelly states that the "oxazolidines . . . are produced as a mixture of diastereomers but these have been separated in some cases and the diastereomers have been shown to be equally useful when carried on in the synthesis," id. at col. 12, lines 55-59, and also states

that "[b]oth oxazolidine isomers are equally effective" in the synthesis of the taxol derivatives, see id. at lines 61-64. It is unclear what diastereomers are produced, but on column 80, the stereoisomer shown is the 4R,5S isomer.

Appellants contend that the diastereomers that are useful in the synthesis disclosed by Kelly are the diastereomers that differ at the 2 position, in which the 4 and 5 positions have opposite stereochemistry, asserting that the diastereomers produced by Kelly are the 2S,4S,5R, the 2S,4R,5S, the 2R,4S,5R and the 2R,4R,5S diastereomers. See Appeal Brief, page 11. If, however, the 4S,5S was produced by the Kelly process as part of the diastereomeric mixture, and was an inherent part of that diastereomeric mixture, the Kelly reference would anticipate the acid of claim 17. See In re Best, 562 F.2d 1252, 1254-55, 195 USPQ 430, 433 (CCPA 1977) ("[W]here the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.")

Although Appellants have argued that the 4S,5S diastereomer would not have been present in the diastereomeric mixture of Kelly, they also state in the Appeal brief that "[a]t a minimum, Appellants' inventive (4S, 5S) intermediates, if made inadvertently, would have been an annoying side product needing to be removed from the desired oxazolidine intermediates." See Appeal Brief, page 12. Although Appellants appear to back away from the position that the 4S,5S isomer

may have been part of the diastereomeric mixture of Kelly, the quoted statement creates an ambiguity in the record that the examiner may want to address.

CONCLUSION

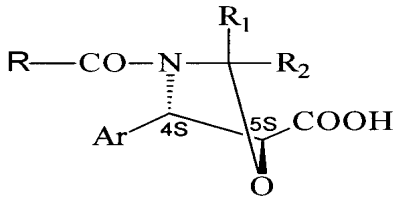
Because the rejections of record, both the obviousness-type double patenting rejection and the rejection under 35 U.S.C. ' 103, failed to set forth a prima facie case of obviousness, they are reversed. Upon receipt of the application, however, the examiner may want to consider the novelty of the claimed compounds in view of the disclosure of Kelly.

REVERSED

William F Smith	)
Administrative Patent Judge	)
	)
	)
	) BOARD OF PATENT
Eric Grimes	)
Administrative Patent Judge	) APPEALS AND
	)
	) INTERFERENCES
	)
Lora M. Green	)
Administrative Patent Judge	)

Appendix

17. An acid of formula (VI) or a salt, ester, anhydride, mixed anhydride, or aldehyde thereof:



(VI)

wherein

Ar represents an aryl radical;

R represents a phenyl radical or a radical R_5-O-, wherein R_5 represents:

-a straight or branched alkyl radical comprising 1 to 8 carbon atoms, an alkenyl radical comprising 2 to 8 carbon atoms, an alkynyl radical comprising 3 to 8 carbon atoms, a cycloalkyl radical comprising 3 to 6 carbon atoms, a cycloalkenyl radical comprising 4 to 6 carbon atoms, or a bicycloalkyl radical comprising 7 to 11 carbon atoms, these radicals being unsubstituted or substituted by at least one substituent selected from a halogen atom and a hydroxyl radical, an alkoxy radical comprising 1 to 4 carbon atoms, a dialkylamino radical in which each alkyl portion comprises 1 to 4 carbon atoms, a piperidino radical, a morpholino radical, a 1-piperazinyl radical (unsubstituted or substituted in the 4-position by an alkyl radical comprising 1 to 4 carbon atoms or by a phenyalkyl radical in which the alkyl portion comprises 1 to 4 carbon atoms), a cycloalkyl radical comprising 3 to 6 carbon atoms, a cycloalkenyl radical 1 to 4 carbon atoms), a cycloalkyl radical comprising 3 to 6 carbon atoms, a cycloalkenyl radical comprising 4 to 6 carbon atoms, a phenyl radical, a cyano radical, a carboxyl radical, and an alkoxycarbonyl radical in which the alkyl portion comprises 1 to 4 carbon atoms, wherein the cycloalkyl, cycloalkenyl or bicycloalkyl radicals are unsubstituted or substituted by at least one alkyl radical comprising 1 to 4 carbon atoms;

-a phenyl radical unsubstituted or substituted by at least one substituent selected from a halogen atom, an alkyl radical comprising 1 to 4 carbon atoms, and an alkoxy radical comprising 1 to 4 carbon atoms; or

-a saturated or unsaturated nitrogen-comprising heterocyclic radical comprising 4 to 6 members and unsubstituted or substituted by one alkyl radical comprising 1 to 4 carbon atoms; and

R_1 and R_2, which are identical or different, represent a hydrogen atom or an alkyl, phenylalkyl, phenyl, alkoxyphenyl, or dialkoxyphenyl, or else R_1 and R_2 form, together with the carbon atom to which they are bonded, a ring having from 4 to 7 members.

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